

Evaluating The Effectiveness Of Combined Drug Therapy In Treating Diabetes

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Abstract

Diabetes mellitus is a chronic, progressive metabolic disorder that often requires aggressive management to prevent long-term microvascular and macrovascular complications. While monotherapy (typically Metformin) is the standard initial approach, it frequently fails to maintain glycemic targets over time due to the progressive decline of pancreatic beta-cell function. Drug combination therapy has emerged as a comprehensive treatment strategy to achieve synergistic metabolic effects and address multiple pathophysiological pathways simultaneously.

Keywords: Diabetes Mellitus; Combined Drug Therapy; HbA1c; Glycemic Control; Synergistic Efficacy.

Introduction

Diabetes mellitus (DM) is primarily characterized by high blood glucose levels (hyperglycemia), polydipsia, and polyphagia. DM is one of the most common metabolic disorders that is increasing at an alarming rate all over the world [1,2,3]. The number of patients with DM has quadrupled (from 108 million in 1980 to 422 million in 2014) within 34 years only, while the worldwide incidence of diabetes among adults over 18 years of age has risen to 8.5% (2014) from 4.7% (1980) [1]. The WHO estimates that diabetes will be the 7th primary cause of fatality by 2030 [2]. There are mainly four common types of DM. Type 1 DM (T1DM) is caused by the autoimmune annihilation of the pancreatic- β cell with no insulin production [4]. This type is also called insulin-dependent diabetes mellitus (IDDM) [5,6]. This type of DM is seen in childhood and includes 5–10% of total diabetes patients [1]. The major type of diabetes is Type 2 DM (T2DM), which is caused due to insufficient production of insulin or desensitization of insulin receptors that precludes the entry of glucose into the cell [7,8]. The type is predominantly seen in 90–95% of cases. There is another type of diabetes called gestational diabetes mellitus (GDM) that occurs only during pregnancy. GDM occurs in approximately 5–15% of pregnant women varying in ethnicity and regions [1,2,3]. Multifarious factors including genetic defects, pancreatic obstruction, surgery, organ transplantation contribute to the onset of this type of diabetes [9]. In the case of 40–60%, women having GDM can develop DM after 5–10 years of pregnancy. Impaired glucose tolerance is potent to be expressed as T2DM whereas uncontrolled diabetes is the potential threat for the onset of other diseases like cardiovascular disease (CVD), blindness, renal failure, neurological disorder, the imbalanced osmolality of blood, hypertension, peripheral neuropathy, and many other diseases [10,11,12,13,14]. Monogenic diabetes, which is often misdiagnosed as T1DM or T2DM is caused by a mutation in a single gene or a cluster of genes [15,16]. It is an autosomal-dominant disease and patients with this have varying signs, symptoms, and clinical courses. The two categories of monogenic diabetes are neonatal DM and familial DM (also known as maturity-onset diabetes of the young (MODY)) [17]. Neonatal DM which is usually developed before 6 months of age can be transient or permanent [18]. The development of familial DM commonly occurs from late childhood through early

adulthood, although it has been diagnosed in adults in their 50s [19,20]. Mutations in genes encoding transcription factors are most common in familial DM. The most common form of familial DM is MODY3 [21]. Clinically, these patients generally have a family history of diabetes, are non-insulin-dependent, and have a low renal threshold for glucose [17].

Pathogenesis of diabetes

T1D is a chronic autoimmune disease in which the immune system mistakenly recognizes insulin-producing β cells as foreign invaders and initiates an attack to β cells (22). Autoreactive T cells, including CD4 and CD8 cells, have been identified as key contributors to the destruction of β cells (23, 24), resulting in the severe loss of β cells, insulin deficiency, and sustained hyperglycemia. Its mechanisms involve innate and adaptive immune responses that might be triggered by the interaction of genetic and environmental factors (25). Genetic factors play a critical role in the pathogenesis of T1D (26), and the genome-wide association studies (GWAS) have provided us a clear understanding of risk genes for T1D (27–29). Variations in specific genes, especially the alleles of the human leukocyte antigen (HLA) gene, primarily class II HLA, could increase the risk of T1D (30). Another important factor associated with the pathogenesis of T1D is environmental effects, which could promote the development of T1D through various pathways, including viral infections (31), gut microbiota (32), and diet, etc. (33). Viral infections, especially those that could destroy β cells or activate the immune system, are considered to be the potential environmental triggers for T1D (34). Additionally, studies have demonstrated that there were significant changes in the composition of gut microbiota in patients with T1D (35, 36), which might be related to the development of T1D (37).

T2D is a heterogeneous progressive disease. Insulin resistance and β cell failure are two main characteristics of T2D, and both of them play crucial roles in disease pathogenesis (38). Insulin resistance refers to a decrease in the metabolic response of target cells to insulin (39). In T2D patients, this means that cells in energy metabolism tissue, including skeletal muscle, the liver, and white adipose tissue, reduce the uptake and processing of glucose, resulting in persistent hyperglycemia (40). For example, skeletal muscle, the largest organ and the primary site for glucose uptake in the human body, was prevented from effectively using insulin, resulting in reduced glycogen synthesis and glucose uptake (41, 42).

The β cell failure is another major indicator of T2D development. It is speculated that the mechanism underlying this decrease in β cell mass might be associated with an increase in β cell apoptosis, and attempting to arrest apoptosis may be a potential therapeutic avenue for T2D (43). The second is caused by the dysfunction of β cells arising from chronic metabolic stress conditions, including endoplasmic reticulum (ER) stress and oxidative stress etc. ER stress may also damage β cells and may even contribute to the development of T2D (44).

Risk Factors for Diabetes

The prevalence of DM has increased and therefore has grown in severity as a public health problem. Multiple risk factors are involved in the actual onset of the disease. Genetics, atmosphere, loss of very first phase associated with insulin launch, sedentary way of life, lack of physical exercise, smoking, alcoholic beverages, dyslipidemia, reduced β -cell sensitivity, hyperinsulinemia, improved glucagon activity are the primary risk elements for prediabetes and DM [45]. These factors appear to play a significant role in insulin resistance or insulin nonfunctionality resulting in disease advancement. Based on WHO (2011), approximately 90% of patients develop T2DM, mostly related to excess body weight. Obstructive sleep apnea and sleep disorder that are seen among overweight adult individuals are a common risk factor for insulin resistance and glucose sensitivity which collectively progresses to prediabetes and then T2DM. The diet containing low fiber but a high glycemic index (GI) is thought to be positively related to the onset of diabetes [46,47].

Dianosis of Diabetes

As untreated DM can lead to serious complications, early diagnosis of diabetes may prevent serious consequences due to the illness. Primary symptoms of diabetes include high blood glucose levels over a prolonged period, frequent urination, increased thirst, and elevated hunger. Some biochemical tests are routinely carried out to make a diagnosis of prediabetes or diabetes. Glycosylated hemoglobin (HbA1c) and

oral glucose tolerance tests (OGTT) are commonly demonstrated for screening diabetes. OGTT test measures how well body cells can absorb glucose after consuming a specific amount of sugar. Usually, the suspected individual is treated with 75 g glucose orally and the plasma glucose level is measured 2 h after ingestion. If the plasma glucose level is found ≥ 11.1 mmol/L, then the individual is diagnosed as diabetic [48]. Fasting plasma glucose test is another reliable routine method for the diagnosis of diabetes. Diabetes patients usually have a fasting glucose level of ≥ 7.0 mmol/L. If a person has a plasma glucose level ≥ 7.8 mmol/L after 2 h of ingesting 75 g glucose, then it is said that the person has impaired glucose tolerance [49]. HbA1c is also widely used as a diagnostic test for diabetes. Patients with T2DM have a glycosylated hemoglobin level of ≥ 48 mmol/mol (≥ 6.5 DCCT%) [50].

Drug combination therapy for T2D

Biguanides + sulphonylureas

Sulphonylureas, a glucose-lowering drug, could be used as an adjunctive drug for metformin in treatment of T2D [51]. In an analysis comparing two different drug combinations, namely sulphonylureas + metformin and DPP4-inhibitors + metformin, the addition of sulphonylureas to metformin demonstrated a higher risk of hypoglycemia and weight gain, indicating that DPP-4 inhibitors may be more suitable than sulphonylureas as adjunctive therapy to metformin for poorly controlled T2D patients [52, 53].

3.3.2. Biguanides + DPP-4 inhibitors

As discussed above, metformin combining with DPP-4 inhibitors is a common drug combination treatment in clinical trials with T2D patients. In a 5-year follow-up trial, it was found that newly diagnosed T2D patients who received early combination therapy with metformin and vildagliptin, a DPP-4 inhibitor, had better long-term glycemic control compared to those who only received early monotherapy with metformin [54]. In addition, it has been reported that the combination of vildagliptin and metformin has a significant association with HbA1c reduction and body weight loss [55].

3.3.3. Biguanides + SGLT2 inhibitors

SGLT2 inhibitors, which are responsible for most glucose reabsorption in the kidneys, play a crucial role in blood glucose regulation for individuals with diabetes (56). Common SGLT2 inhibitor drugs include canagliflozin, dapagliflozin, empagliflozin, janagliflozin, etc.

3.3.4. Biguanides + GLP-1 receptor agonists

GLP-1 receptor agonists (GLP-1RAs), such as lixisenatide, exenatide, liraglutide, and semaglutide, have been widely utilized in the therapy of T2D due to their advantages in blood glucose control, weight loss, and protection of pancreatic β cells, etc (57, 58). In studies evaluating the impact of the combination therapy with exenatide and metformin on patients with T2D, it was found that compared with the placebo-metformin group, the group of exenatide-metformin showed better glucose and body weight control (59).

3.3.5. Biguanides + TZDs

Thiazolidinediones (TZDs), also known as glitazones, are a class of insulin sensitizers primarily used for the treatment of T2D (60). They are responsible for regulating insulin sensitivity, helping cells better respond to insulin and effectively utilize glucose (61).

3.3.6. Biguanides + alpha glucosidase inhibitors

A study comparing the effects of the combination of acarbose (alpha glucosidase inhibitors) and metformin therapy with acarbose monotherapy in the treatment of T2D reported that the combination treatment could greatly improve glycemic control in T2D individuals with a significant reduction in HbA1c, fasting plasma glucose, and postprandial glucose compared to baseline ($p < 0.0001$). Additionally, the combination therapy was superior to monotherapy in weight control without increasing the hypoglycemic risk (62).

3.3.7. Insulin + sulphonylureas

For many poorly controlled T2D patients who only received insulin monotherapy, clinical doctors may also recommend they to use some oral anti-diabetic medications at the same time. In a retrospective study, researchers found that the combination of insulin and oral glimepiride (sulphonylureas) in patients with

T2D showed a more significant improvement in HbA1c control compared to insulin alone, decreasing from 8.5 +/- 0.6% to 7.4 +/- 0.8% (P < 0.0001).

3.3.8. Insulin + DPP-4 inhibitors

When Sitagliptin, a DPP-4 inhibitor, was added to insulin therapy in the treatment of poorly controlled patients with T2D, it was found that the combined group had a greater reduction in HbA1c level compared to the group with increased insulin dose. Moreover, there were fewer adverse effects in the combined group, including lower frequency and severity of hypoglycemic events, as well as less weight gain (63).

3.3.9. Insulin + SGLT2 inhibitors

In a 78-week clinical trial for assessing the efficacy and safety of adding empagliflozin to basal insulin therapy in patients with poorly controlled T2D, individuals were randomly assigned to different doses of empagliflozin (10mg or 25 mg) or a placebo group. Results indicated that the addition of empagliflozin could significantly improve blood glucose management in T2D patients with inadequate basal insulin control. This combination therapy not only reduced HbA1c levels and insulin dosages, but also contributed to weight control and systolic blood pressure reduction (64).

3.3.10. Insulin + GLP-1 receptor agonists

A meta-analysis exploring the efficacy of combining lixisenatide with basal insulin revealed that, compared with insulin monotherapy, this combination treatment could effectively reduce HbA1c levels, particularly in controlling postprandial glucose (PPG). However, there were no notable differences in fasting plasma glucose (FPG) levels between these two groups. Insulin could effectively control FPG, but further oral management is required for optimal control.

3.3.11. Insulin + TZDs

In many clinical trials, insulin combined with pioglitazone (TZDs) has been widely utilized to treat T2D patients. For example, in a study exploring the benefits of insulin plus pioglitazone in poorly controlled T2D patients, this combination therapy not only improved blood glucose levels and reduced daily insulin dosages, but also had a positive effect on lipid level control, suggesting that the co-administration of insulin and pioglitazone could improve the therapeutic effects of diabetes patients in multiple aspects (65).

3.3.12. SGLT2 inhibitors + DPP-4 inhibitors

It was reported that the combination of empagliflozin (SGLT2 inhibitors) and linagliptin (a DPP-4 inhibitor) could provide more effective hypoglycemic effects than monotherapy in patients who did not respond to metformin, with a lower risk of hypoglycemia (65).

3.3.13. DPP-4 inhibitors + TZDs

In a clinical trial evaluating the effect of a combination of alogliptin (a DPP-4 inhibitor) and pioglitazone (a TZD) in treating drug-naïve patients with T2D, the combination treatment showed more significant reductions in HbA1c levels and fasting blood glucose levels than monotherapy alone. Moreover, the safety of the combination therapy was consistent with that of monotherapy.

3.3.14. Other drug combination options

In addition to the combination of certain medications discussed above, there are numerous other dual-combination approaches for the treatment of T2D, including combinations of alpha glucosidase inhibitors and DPP-4 inhibitors, SGLT2 inhibitors and GLP-1 receptor agonists.

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